MSN Life Sciences Private Limited

LS3 TSD Activities for FY 2024-25

MSN Life Sciences Pvt. Limited
Date: 27-03-2025

Troubleshooting/ Improvements in N

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S.#	Product & Stage	Description	Troubleshooting/ Improvement	Remarks
1	Atogepant- All stages	Scale-up	Scale-up with double batch size in all the four stages (AOGT1, AOGT2, AOGT3 & AOGT4) to meet the customer requirement	
2	Vericiguat- VRGT1	Agitator Modification	As per process requirement based on nature of reaction mass, Installed the Hydrofoil agitator for I/SSR/38 in place of anchor for reaction	
3	Samidorphan L-Malate- SPLA1	Scale-up	Batch size increase from 14 kg to 40 kg in SPLA1 to release the small equipment for other product and to fast up the campaign for next stages.	
4	Vonoprazan Fumarate- VPNA4	Scale-up	Batch size increase from 24 kg to 40 kg in VPNA4 to meet the customer requirement on priority basis.	
5	Romidepsin-RDPC5	AIUI impurity issue	AIUI impurity issue was resolved in RDPC5 stage of Romidepsin by increasing the IPA quantity from 2 volumes to 3 volumes during product Isolation.	
6	Atogepant-AOGT1	formation of BOC impurity which was causing HIUI failures	Investigated and identified the reason for formation of BOC impurity, which was causing HIUI failures, & by optimizing the addition of BOC anhydride based on the wet material Quantity.	
			N-Heptane slurry was introduced in addition to the process, whenever there is spike in MSI at AOGT1 to control the MSI at initial stages itself	
7	Atogepant-AOGT1	Yield improvement	Yield improved from 0.29 w/w to 0.37 w/w in AOGT1 stage of Atogepant by quantifying the distillation operation and avoiding the emulsion formation during work-up.	
8	Romidepsin-RDPC3 & RDPC6	Yield improvement	Yield improved from 0.56 w/w to 0.68 w/w in RDPC3 & from 0.5 w/w to 0.65 w/w in RDPC6 stage by following necessary precaution at Cryo reaction followed by quenching & Work-up operations	
9	Vonoprazan Fumarate- VPNA3	Yield improvement	Yield improved from 0.61 w/w to 1.03 w/w by following necessary precaution at MMA Assay NLT 35% followed by Reaction mass after Distillation fixed quantity, Complete Liquor Ammonia charging and finally after distillation residue monitoring	

Capacity Enhancement or Release

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Product: Flecainide Acetate
Scale-up Proposal

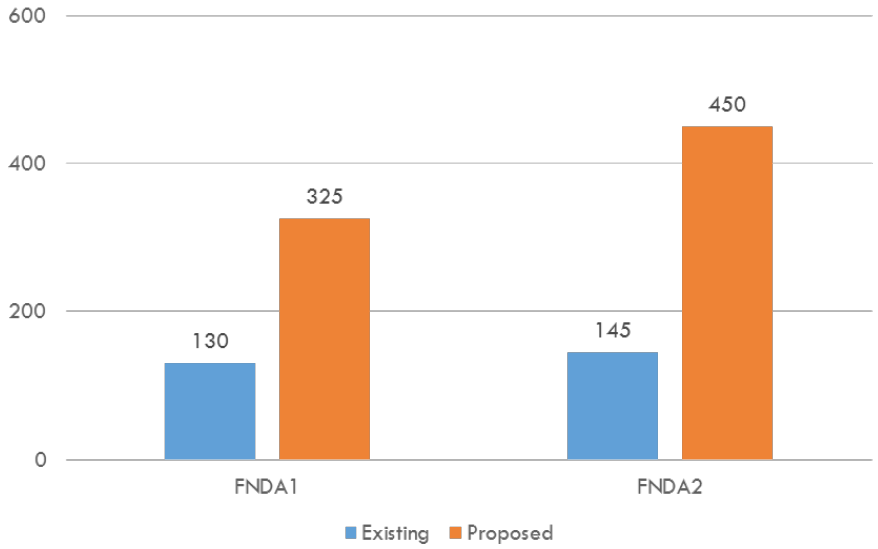
- **FNDA1:** Scale-up from 130 Kg to 325 Kg in existing B-Block facility,
- **FNDA2:** Scale-up from 145 Kg to 450 Kg in existing F-Block Phase-IV.

Existing: 1.07 TPM. & **Proposed:** 4.30 TPM.

Challenges:

Drying temperature @ 30±5°C, Acetic Acid Content spec narrow range (12.4-12.8% w/w) & Toluene removal (NMT 890 ppm)- **Dry Vacuum Pump Proposed.**

FNDA1		FNDA2	
Existing	Proposed	Existing	Proposed
130 Kg	325 Kg	145 Kg	370 Kg



Current Status:

Stage-1 (FNDA1) & Stage-2 (FNDA2) Scale-up Validation completed.

Total Release of ~1795 KL Days (~60%)

Capacity Enhancement or Release

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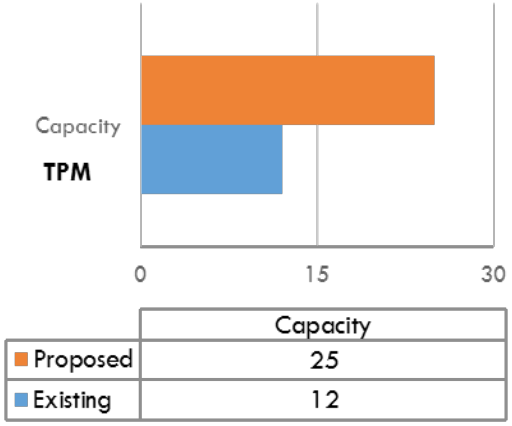
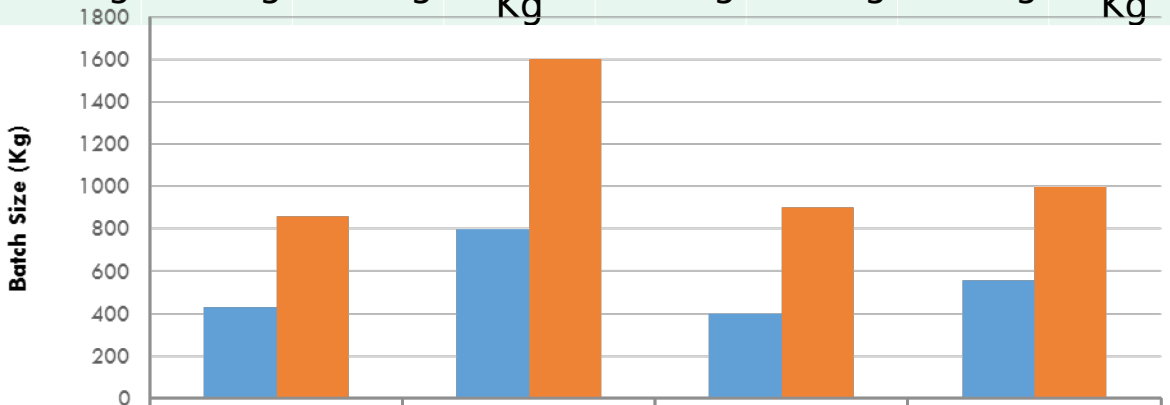
Product: Pregabalin

Scale-up Proposal



	Capacity
Proposed	25
Existing	12

PBLN1		PBLN2		PBLN3		PBLN4	
Existing	Proposed	Existing	Proposed	Existing	Proposed	Existing	Proposed
431 Kg	862 Kg	800 Kg	1600 Kg	400 Kg	900 Kg	560 Kg	1000 Kg



	PBLN1	PBLN2	PBLN3	PBLN4
Existing	431	800	400	560
Proposed	862	1600	900	1000

Stage	Proposal				Capacity (TPM)		Current Status
	Existing		Proposed		Existing	Proposed	
	B.Size (Kg)	Location	B.Size (Kg)	Location			
PBLN1	431	A-Block	862	C-Block	12	25	Validation Completed
PBLN2	800	A-Block	1600	C-Block			Validation Completed
PBLN3	400	A-Block	900	C-Block			Validation Completed
PBLN4	560	F-I	1000	G-1			Validation to be planned.

Trouble shooting

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Delayed Crystallization in Opicapone API To Meet Desired Bulk Density	
Product & Stage:	**Opicapone API (OCPN6)**
Existing Situation	**Requirement**
Opicapone Pharma material Bulk Density obtained was ~0.07-0.09 gm/ml in existing process.	As per customer (Abbott) requirement, Bulk Density should be more than 0.11 gm/ml.
Proposal:	
Experiments were conducted at PD Lab to achieve desired Bulk Density by modifying various parameters. As per the executed batches observation, slow addition of methanol for anti-solvent crystallization observed higher bulk density in previous campaign. Based on above observation, crystallization was delayed by adding only 10% of the anti solvent slowly at 62±1°C, maintain for 60 min followed by adding remaining 90% of solvent slowly in 60-120 min.	
Results & Way forward:	
As per the modified process, re-process was taken for previous batches and the bulk density is meeting the requirement. Product Specific SOP was created for slow addition of Methanol Lot-1 (Anti solvent) to address the customer query. Same process was followed for next campaign during API manufacturing to get the desired Bulk Density, 5 batches were dispatched with the proposed process.	

Trouble shooting

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Solubility Concern in Metoprolol Tartrate from Metoprolol Freebase	
Product & Stage:	**Metoprolol Tartrate & MPLT1**
Existing Situation	**Requirement**
As per initial Process Metoprolol Tartrate was manufactured from Succinate salt by succinate salt breaking followed by tartrate salt formation. New Process was given by LS-3 R&D for Tartrate salt manufacture directly from Metoprolol Freebase.	Solubility of API material from new process in not meeting in MDC & Chloroform solvents.
Proposal:	
Experiments were conducted at PD Lab to meet the solubility, as per discussion with senior team, Free base was dissolved in MDC, filtered through millpore paper for junk filtration followed by distilled and tartrate salt formed as per proposed process in IPA solvent. Material is meeting the solubility in Lab scale, hence experimental batch was proposed at I-Block facility.	
Current Status:	
10 Kg Experimental batch was executed at I-Block with MDC Slurry of Free Base followed by junk free filtration before regular process. Obtained yield (0.83 w/w) is acceptable. Solubility issue was resolved but GTI impurity (Epoxy Ether Impurity) in final material was 3.92 ppm against the specification limit of NMT 2.9 ppm. Additional purification with 3.0 Vol of IPA was checked at PD Lab to check the impurity purgeability.	

Liq. Nitrogen in place of Dry Ice in Finerenone

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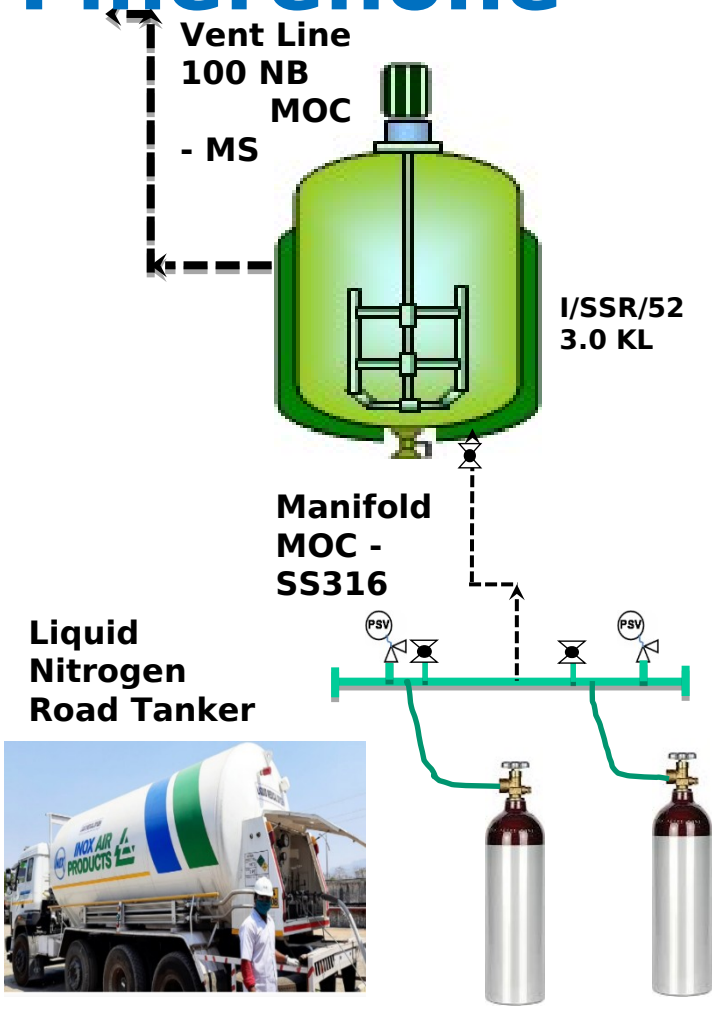

Liquid Nitrogen Vs Dry Ice for Fineranone Product									
S.#	Utility	Latent Heat		Total Qty /Campaign		Heat Load	Cost		Total Cost
		KJ/Kg	Kcal/Kg	Kg	Nm3	Kcal	Rs/Kg	Rs/m3	Lakhs
1	Liq. N2	200	47.8	15576	12585	744533	--	30	3.78
2	Dry Ice	571	136.5	5456	--		21	--	1.15

Dry Ice is Not Suitable for Highly exothermic & Rapid cooling requirements. Hence Liquid Nitrogen was used for FRNE5 stage of Finerenone.

Design & Safety Improvements at I-S III

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S.#	Product & Stage	Design Improvements	Action plan	Remarks
1	Samidorphan L-Malate (SPLM3)	Sparkler filter for Carbon treatment	Sparkler Filter was used in-place of Leaf filter for Carbon filtration in SPLM3 stage of Samidorphan L-Malate.	
2	Vonoprazan Fumarate (VPNA3) & Fineranone (FRNE5)	Jacketed receivers for External cooling with Dry ice + Methanol	1.0 KL & 0.3 KL Jacketed receivers for External cooling circulation system with Dry ice + Methanol was installed in I-Block. This system was used in VPNA3 stage of Vonoprazan Fumarate during Reduction reaction with M-070 (Sodium Borohydrate) at -10±5°C & in FRNE5 stage of Fineranone during reaction with H2SO4 at -15±5°C.	
3	Medetomidine, MEDT1	Dump tanks for critical reactions	Dump tanks were installed in F-Block & B-Block for critical reaction reactors (Grignard, Hydrogenation & Bromination) in Medetomidine product.	
4	Medetomidine, MEDT4	New Scrubber for Bromine	New Scrubber was procured & installed at F-Block for Bromine handling in MEDT4 stage of Medetomidine.	
5	Romodepsin, RDPC5	Pyrophoric reagent (DIBAL-H) addition	Suitable facility was created for DIBAL-H reagent addition in RDPC5 stage of Romodepsin at I-Block.	
6	Samidorphan L-Malate (SPLM3)	Carbon Monoxide detector for pressure reaction	Carbon Monoxide detector was arranged as part of safety during pressure reaction (4 to 5 Kg/Cm2) in SPLM3 stage of Samidorphan L-Malate.	

Projects Related Activities at LS-III

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S.#	Block	Activity	Remarks
1	G-Block	Utility capacities (CT Water, Chilled water, Brine, etc.)	Utility load calculated and proposed capacities submitted to ESD Department.
2	SRS Area	Proposal for Continuous Distillation column.	Installation completed, trials to be taken
3	H,I,L,K &J-Block Tank Pad	Phase-1 Tanks list finalised for I-Block	Plant sign-off completed, further approval pending
4	G-Block	Filtration & Drying equipment finalization for Capacity enhancement of Pregabalin, Clopidogrel Bisulfaate, Rosuvastatin Calcium & Atorvastatin Calcium in G-Block.	Discussion completed with Subba Rao sir and Drier capacities finalised as per specific product requirement. **Phase-1:** Pregabalin (5 KL ANFD followed by 4 KL RCVD) **Phase-2:** Rosuvastatin Calcium (60" x 2 Nos Followed by 2.5/3.0 KL RCVD- 2 Nos) **Phase-3:** Clopidogrel Bisulfate (60" x 2 Nos Followed by 3 KL RCVD, 96 Trays VTDR- 1 No. for other products) **Phase-4:** Atorvastatin Calcium (60" x 2 Nos Followed by 192 Trays x 1 Drier)
5	NA	Vacuum pumps Selection Philosophy and Standard P&ID for Vacuum set-up in upcoming projects.	Vacuum pumps selection matrix prepared and circulated to CFT.

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Thank you